

REMARKS

I. Interview

Applicants thank the Examiner for the courtesy of a telephonic interview with Applicants' undersigned attorney and Jeffrey Sears, Assistant General Counsel for Columbia University. The latest Office Action, the Lee and Nevo references, and certain possible changes to the claims were discussed during the interview, as will be discussed in more detail below.

II. Claim Amendments

In the amendments above, Claims 1, 6-16, 18-20, 22-30, 36-43, 45, 47-52, and 54-63 have been amended and new Claims 64-82 have been added, to more particularly point out and distinctly claim Applicants' invention. Support for the newly added claims can be found, for example, in Claims 1, 6-18, 29, 33, 61, and 62 in paragraphs 59 and 67 (of the publication).

III. § 112 Rejection

Claims 43 and 44 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner maintains that in Claims 43 and 44, the "fluid pressure" lacks antecedent basis. The Examiner's attention is directed to the newly added claims above, particularly Claims 96 and 97, which are dependent upon Claim 91. There is an antecedent basis for "fluid pressure" in Claim 91.

IV. §102(b) Rejection

Claims 1-5, 13-19, 22-35, 58-60 and 62 have been rejected under 35 U.S.C. §102(b) as being anticipated by Lee et al., PCT Publication No. WO 98/40111 ("Lee") as

evidenced by Lee et al., Journal of Orthopaedic Research ("Lee and Bader"). The Examiner maintains that with respect to Claim 29, Lee discloses a method for producing functioning cartilaginous tissue from a cell-seeded scaffold or a cell-seeded scaffold integrated with a osteoconductive and/or osteoinductive substrate, wherein the method includes inoculating chondrocytes into a scaffold or biocompatible substrate, placing the cell-seeded scaffold or substrate into a bioreactor, applying a strain-controlled deformational loading to the seeded scaffold or substrate vial loading platens according to a load regime optimized for cartilaginous tissue growth, and culturing the scaffold or substrate for a time sufficient to produce functional cartilaginous tissue; that Lee and Bader is cited as evidence that the bioreactor employed in Example 10 includes loading platens and control electronics for providing the strain-controlled deformational loading of the scaffolds or substrates; that the use of multiple references in a 35 U.S.C. §102 rejection is proper when the extra reference provides evidence of what already exists in the primary reference; that with respect to Claims 1, 30 and 62, the bioreactor employed by Lee includes a growth chamber and means for applying strain-controlled deformational loading via loading platens; and that with respect to Claims 2-5 and 22-28, in the absence of further positively recited structure of the device, the system of the primary reference is considered to be capable of producing and/or operating [on] tissue as recited in these dependent claims.

The Examiner also maintains that with respect to Claims 13-19, the system of the primary reference is structurally capable of providing the loading regimes of Claims 13-19; that with respect to Claims 31-34, Lee discloses that the substrate material can be biodegradable, bioresorbable, biocompatible and/or non-resorbable; that with respect to Claim 35, the implant material resulting from the treatment disclosed by Lee is considered to produce an implant material with the claimed properties of Claim 35; and that with respect to Claims 58-60, the bioreactor and/or platens are capable of producing tissue of a desired shape that can be implanted.

V. § 103(a) Rejections

Claims 45-51 and 54-57 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Lee as evidenced by Lee and Bader. The Examiner maintains that with respect to the strain loading of Claims 45-51, Lee discloses that the object of the treatment system is to expose the tissue constructs to loading that resembles the physiological conditions typically encountered by the tissue being replaced and/or repaired; that in view of this teaching, it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the typical conditions that the desired tissue would be exposed to in order to mimic those physiological conditions in terms of loading, frequency and length of time; and that with respect to Claims 54-57, while Lee discloses that the implant is used for repair of damaged connective tissue, the reference is silent with respect to the specifics of the implant; and that, however, in the absence of a showing of criticality and/or unexpected results, it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the specific type of cartilage produced based merely on the [intended] use of the cartilage in terms of the location in the body [where] it is intended to be implanted.

Claims 6-12, 20, 21, 36-44, 52, 53, 62 and 63 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Lee as evidenced by Lee and Bader taken further in view of Nevo et al., U.S. published application No. 2002/0009805 ("Nevo"). The Examiner maintains that with respect to Claims 6-12, 20, 21, 36-44, 52, 53, 62 and 63, while Lee discloses that hydrostatic pressure is a known means for loading tissue implants prior to implantation, the instant claims require the combination of the strain and hydrostatic loading; that Nevo discloses that it is known in the art to maintain tissue constructs under culture conditions that control hydrostatic pressure that the tissue is exposed to; that in view of this teaching, it would have been obvious to one of ordinary

skill in the art at the time the invention was made to modify the system of the primary reference to include hydrostatic loading as suggested by Nevo for the known and expected result of providing an additional means recognized in the art for ensuring that the cultured cells are exposed to conditions that mimic physiological conditions and for improving the contact of the culture medium within in pores of the porous scaffold material during the culture process; and that with respect to the specific loading conditions, it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the typical conditions that the desired tissue would be exposed to and operate the device to mimic those physiological conditions in terms of loading, frequency, and length of time.

VI. Discussion

Applicants respectfully traverse the above rejections.

Applicants' independent Claim 1 is directed to a bioreactor for producing functional cartilaginous tissue from a cell-seeded scaffold. Among other things, independent Claim 1 includes a growth chamber, a means for applying strain-controlled deformational loading, and a means for controlling that loading according to a loading regime for producing functional cartilaginous tissue.

Neither Lee nor Lee and Bader teaches or suggests a bioreactor including, among other things, a means for controlling strain-controlled deformational loading according to a loading regime for producing functional cartilaginous tissue. Lee and Lee and Bader each produce a final tissue product after 48 hours of applied deformational loading. (See, e.g., Lee examples 6 and 10 and Lee and Bader "Results" section.) However, as explained in detail in the declaration of co-inventor Clark Hung submitted herewith, neither Lee nor Lee and Bader provides any quantifiable evidence from which one of ordinary skill in the art could or would conclude that the final tissue

products in Lee and Lee and Bader are functional cartilaginous tissue, i.e., tissue with functional properties as defined in Applicants' published application:

"possessing the mechanical, electrical, chemical and biochemical properties of cartilaginous tissue - the properties that permit cartilage to perform its load-bearing capacity." (Paragraph 29.)

Specifically, as explained in the declaration, Lee does not provide any quantifiable evidence of any mechanical, electrical, chemical, or biochemical properties customarily considered by those of ordinary skill in the art to evaluate whether a tissue product is functional cartilaginous tissue. As also explained in the declaration, Lee and Bader do provide quantifiable evidence of a single biochemical property (namely, GAG content), but the value of that property is several orders of magnitude lower than the threshold of that property generally considered by those of skill in the art to be indicative of functional cartilaginous tissue. In summary, neither Lee nor Lee and Bader teach or suggest the production of functional cartilaginous tissue. Since neither Lee nor Lee and Bader teach or suggest the production of functional cartilaginous tissue, Lee and Lee and Bader cannot and do not teach or suggest a loading regime for producing such tissue. Lee and Lee and Bader do not, therefore, teach or suggest a bioreactor including, among other things, a means for controlling strain-controlled deformational loading according to a loading regime for producing functional cartilaginous tissue.

Nevo does not remedy the deficiencies of Lee and Lee and Bader. Specifically, Nevo describes only the application of hydrostatic pressure, and does not contain any disclosure related to application of strain-controlled deformational loading. Since Nevo does not teach or suggest strain-controlled deformational loading, Nevo cannot and does not teach or suggest a means for controlling that loading. Nevo does not, therefore, teach or suggest a bioreactor including, among other things, a means for controlling strain-controlled deformational loading according to a loading regime for producing functional cartilaginous tissue.

Accordingly, independent Claim 1 is allowable over the cited prior art. Since independent Claim 1 is allowable, Claims 2-28, 36, 37, 62, 65, 68, 71, 77, and 78 depending therefrom are also allowable based at least on their dependency from Claim 1.

Applicants' independent Claims 29, 61, and 74-76 are directed to methods, bioreactor systems, and bioreactors and include features similar to those of independent Claim 1. Independent Claims 29, 61, and 74-76 are therefore allowable at least based on the arguments previously provided herein with respect to independent Claim 1. Since independent Claims 29 and 61 are allowable, Claims 30-35, 38-60, 63, 64, 66, 67, 69, 70, 72, 73, and 79-82 depending therefrom are also allowable at least based on their dependency from Claims 29 and 61.

In the Office Action, claims in the instant application were rejected under both §102 (b) and §103(a) as being unpatentable over Lee and Lee and Bader. Applicants respectfully disagree that two references can be combined to support a §102(a) rejection, as the Examiner has done. As is set forth in M.P.E.P. §2131.01, a §102 rejection based on multiple inferences is proper when the extra reference is cited to:

- (A) Prove the primary reference contains "an enabled disclosure;"
- (B) Explain the meaning of a term used in the primary reference; or
- (C) Show that a characteristics not disclosed in the reference is inherent.

The Examiner's rationale that the combination of references to support a §102(b) rejection is proper because Lee and Bader "provides evidence of what already exists in" Lee does not meet any of criteria (A) to (C). Rather, the Examiner is using Lee and Bader to show the construction of a bioreactor that is vaguely mentioned in Lee but not shown in sufficient detail so that one skilled in the art would appreciate its construction. Moreover, to the extent that criterion (C) is the closest, one skilled in the art would not

inherently know from Lee that the bioreactor in Lee contained loading platens and electronics.

In sum, the subject matter of the claims herein, especially as amended above, is not suggested or disclosed by Lee, Lee and Bader, and/or Nevo. Accordingly, the rejections under §102(b) or 103(a) should be withdrawn.

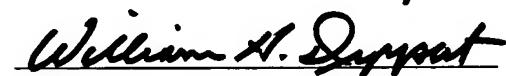
Applicants again thank the Examiner for the courtesy of the telephonic interview mentioned above.

Should the claims herein be allowable but for minor matters that could be the subject of either a supplemental response or an Examiner's Amendment, Applicants would appreciate the Examiner's contacting Applicants' undersigned attorney of record.

Reconsideration and allowance of all the claims herein are respectfully requested.

Respectfully submitted,

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